

## REMARKS

### Status of Claims

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 2, 3, 5, 6, and 51-53 have been canceled, and claims 1, 4, 7, and 8 have been amended. Claims 9-50 have been withdrawn. Therefore, claims 1, 4, 7, and 8 are currently under examination. Support for the amendments to claim 1 can be found in original claims 2-3 and 5-6. The dependencies of claims 4, 7, and 8 have been amended due to the cancellation of claims 2-3 or 5-6. Reconsideration of the pending application is respectfully requested.

### Interview Summary

Applicant's representative thanks Examiner Wessendorf for the courtesies extended to her during the interview of July 26, 2004.

During the interview it was clarified that the executed Declaration was located in the official file wrapper at the U.S. Patent and Trademark Office. Examiner Wessendorf indicated that a substitute copy of the executed declaration was not necessary. The art rejections were also discussed during the interview.

### Objection to the Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 76, line 9. The paragraph beginning at page 76, line 6 has been amended to remove the hyperlink, thereby addressing this objection.

### Oath/Declaration

The office action indicated that the oath or declaration is defective because it was not executed. During the examiner interview on July 26, 2004, the examiner indicated that this rejection was withdrawn.

35 U.S.C. §112, First Paragraph

Claims 51-53 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Claims 51-52 have been cancelled thereby rendering this rejection moot.

35 U.S.C. §112, Second Paragraph

Claims 1-8 and 51-53, are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The examiner indicates the in claims 1 and 51-52 the term "more" is indefinite. The examiner suggests that "more" be replaced with the term "at least." Applicant respectfully disagrees with examiner regarding the indefiniteness of the term "more," but in order to expedite prosecution, Applicant has replaced the term in claim 1 as suggested.

Double Patenting

Claims 51-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7 of U.S. Patent No. 6,673,901. Claims 51-52 have been cancelled thereby rendering this rejection moot.

The 35 U.S.C. §102 Rejections

Claims 1-3, 5-6, 8, and 51-52 are rejected under 35 U.S.C. §102(b) as being anticipated by Lipovsek (WO 00/34784) for the reasons advanced in the last office action. Claim 1 has been amended, and claim 8 has been amended to depend from claim 1. Claims 2-3, 5-6 and 51-52 have been cancelled. Insofar as this rejection is applied to currently pending claims 1 and 8, it is hereby traversed.

Claim 1 has been amended to recite a modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue.

Lipovsek discloses that the loop regions can be modified to prepare new compound-binding proteins. Lipovsek postulates that the randomization of loops are "unlikely to have an adverse effect on the overall fold or stability of the <sup>10</sup>Fn3 framework itself" (page 15, lines 4-6). Lipovsek, however does not teach or suggest a way to make the test molecule more stable. It appears that Lipovsek did not even consider the possibility of improving the stability of the Fn3 framework as compared to the wild-type molecule; Lipovsek simply did not want the molecule to lose stability. Further, it is important to note that Lipovsek does not teach or suggest introducing a stabilizing mutation by substituting at least one of the specific residues Asp 7, Asp 23 or Glu 9 with another amino acid residue. Nowhere in the publication does Lipovsek teach that the substitution of any of these three residues would stabilize the molecule as compared to a wild-type Fn3.

Since all of the features of the claimed invention are not disclosed by Lipovsek, the publication does not anticipate the claimed subject matter. Therefore, Applicant respectfully requests withdrawal of this rejection of the pending claims 1 and 8 under 35 U.S.C. § 102(b).

35 U.S.C. §103(a)

Claims 1-8 and 51-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lipovsek (WO 00/34784) in view of Koide (WO 98/56915) and Blaschuk (U.S. 6,391,855) for reasons set forth in the last office action. Claims 2-3, 5-6 and 51-52 have been cancelled. Insofar as this rejection is applied to currently pending claims 1, 4, 7, and 8, it is hereby traversed.

As discussed above, Lipvosek does not generally teach or suggest making a molecule more stable than its corresponding wild-type molecule. Nor does Lipvosek specifically teach or suggest introducing a stabilizing mutation into Fn3 by substituting at least one of the particular residues Asp 7, Asp 23 or Glu 9 with another amino acid residue. Neither Koide (WO 98/56915) nor Blaschuk (U.S. 6,391,855) remedy the deficiencies of Lipvosek.

Koide at page 54, at lines 4-5, refers to a Dickenson *et al.* reference that proposed that Val 29 and Arg 30 play a role in stabilizing the native Fn3. Koide continues (at page 54, lines 10-15) by mentioning that certain mutations in the FG loop may have less impact on stability, and that mutations in the N-terminal tail would not be expected to have strong detrimental effects

on stability. Thus, Koide discussed trying to minimize adverse effects of mutations to Fn3. Koide did not discuss trying to improve stability of native Fn3. Further, Koide does not specifically teach or suggest introducing a stabilizing mutation into Fn3 by substituting at least one of the particular residues Asp 7, Asp 23 or Glu 9 with another amino acid residue.

Blaschuk does not remedy the deficiencies of Lipovsek or Koide. Blaschuk generally discusses conservative substitutions, in particular conservative substitutions where the secondary structure and hydrophobic nature of the polypeptide is substantially unchanged. There is no teaching in Blaschuk that a conservative substitution would improve stability. Further, Blaschuk does not specifically teach or suggest introducing a stabilizing mutation into Fn3 by substituting at least one of the particular residues Asp 7, Asp 23 or Glu 9 with another amino acid residue.

Since the cited references, neither singly or in combination, teach or suggest all of the features of the claimed invention, a *prima facie* case of obviousness has not been established. Withdrawal of the rejection of claims 1, 4, 7, and 8 under 35 U.S.C. § 103(a) is therefore respectfully requested.

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Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 337-2540 to facilitate prosecution of this application.

Enclosed is a check for the Petition for a One-month Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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